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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference VA/H-32534A	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/07602	International filing date *(day/month/year)* 14.07.2003	Priority date *(day/month/year)* 15.07.2002
International Patent Classification (IPC) or both national classification and IPC C07K14/305		
Applicant NOVARTIS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

EPO - DG 1

17. 12. 2004

3. This report contains indications relating to the following items:

   I ☒ Basis of the opinion
   II ☐ Priority
   III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   IV ☐ Lack of unity of invention
   V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   VI ☐ Certain documents cited
   VII ☐ Certain defects in the international application
   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14.01.2004	03.11.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Heiduschat, C Telephone No. +49 89 2399-7804

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/07602

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-26 as originally filed

Sequence listings part of the description, Pages

1-6 as originally filed

Claims, Numbers

1-30 as originally filed

Drawings, Sheets

1/3, 2/3, 3/3 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,2,6,9,10,15,23,27-29
	No:	Claims	3-5,7-8,11-14,16-22,24,25,30
Inventive step (IS)	Yes:	Claims	none
	No:	Claims	1-30
Industrial applicability (IA)	Yes:	Claims	1-30
	No:	Claims	none

2. Citations and explanations

   see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) The Application

The present application is based on the cloning of hsp70 of Arthrobacter, which may be useful in imunostimmulatory compositions and vaccines.

2) The Prior Art

Reference is made to the following document/s/:

D1: WO-A-0129233
D2: WO-A-0204018
D3: WO-A-0168865
D4: Newport GR, Seminars In Immunology, W.b. Saunders Company, Pa, Us (1991), 3(1), 17-24
D5: Gudding R et al., Veterinary Immunology And Immunopathology, Amsterdam, Nl (1999), 72, 203-212
D6: WO 01 10469 A (RITCHIE RACHEL JANE ;GRIFFITHS STEVEN (CA); AQUA HEALTH EUROP LTD) 15 February 2001 (2001-02-15) cited in the application
D7: Kuzyk MA et al., Vaccine, Butterworth Scientific. Guildford, Gb (21-03-2001), 19(17-19), 2337-2344
D8: US-A-5 858 773 (MAZODIER PHILIPPE ET AL) 12 January 1999 (1999-01-12)
D9: WO-A-9833884
D10: Koch et al., Fems Microbiology Letters, Amsterdam, Nl (1994), 123(1/2), 167-171

3) Novelty (Article 33(2) PCT)

The hsp70 sequences SEQ ID NO:1 and 2 are considered novel. However, in view of the high similarity of sequences within the hsp70-family it cannot be excluded that fragments of other hsp70 are identical to certain fragments of Arthrobacter hsp70. As claims 3 and 11 refer to sequences comprising such fragments hsp70 proteins of other organisms are encompassed by these claims. Same applies to an antibody against such vaguely defined fragments. A hsp70 sequence of other bacteria e.g. Mycobacterium tuberculosis (e.g. D1 and D2) may be understood as comprising a fragment according to claim 3 or 11 or even as a "derivative" according to claim 11. D1 and D2 are both considered novelty destroying to claims 3, 7, 8, 11, 16, 17, 18, 21, 24 and 25 based on such "fragment" or "derivative". D1 further discloses fusion proteins of hsp70 with antigens of other pathogens, thus it is additionally considered novelty destroying to claims 4, 5, 12 to 14, 19, 20 and 22.
D3 discloses several antigens derived from Piscirickettsia salmonis, among others a hsp70

protein (SEQ ID NO:18, p.12-13), which are suggested for the preparation of vaccines against the infection of fish by Piscirickettsia salmonis. Thus, D3 is considered novelty destroying to claim 30.

4) Inventive Step

4.1 The present application is based on the cloning of a surface antigen hsp70 of Arthrobacter and its use in the preparation of vaccines.

4.2 D4 describes the usefulness of heat shock proteins for the stimulation of immune response. Arthrobacter (strain ATCC 55921) had been found useful as immunostimulatory agent and live vaccine against Bacterial Kidney disease (BKD) in fish (D8) which is caused by a closely related bacterium Renibacterium salmoninarum. However, it was suggested, that its protective effect was based on stimulation of unspecific and specific immunity by infection of the same cell-type as by the pathogen R. salmoninarum. Several general strategies applied in fish-vaccinology are discussed in D5. A vaccine to P. salmonis based on a 17kD surface protein thereof is described in D7. However, none of these documents, alone or in combination, provides any incentive to identify the sequence of hsp70 of Arthrobacter or suggest its usefulness in the vaccination of fish.

4.3 In the light of the prior art the technical problem to be solved can be seen as the provision of a polypeptide which can enhance the protective effect of vaccines.
The solution of this problem provided by the Applicant is the provision of a hsp70 polypeptide and the DNA-Sequence encoding it. Vaccine compositions comprising whole or certain parts of hsp70 amino acid or DNA sequence of Arthrobacter in addition to further antigens appear to be more effective than certain conventional vaccines comprising only an antigen of the pathogen. Therefore, the above mentioned technical problem is solved. However, this solution is not represented by any of the claims.

4.4 Claims 1 to 3 and 9 to 11 refer to fragments of the hsp70 polypeptide of Arthrobacter. Such fragments could also be derived from other already known hsp70 proteins (see also item 3; D1, D2 or D4). Furthermore, it is not credible that all possible fragments of hsp70 show the same surprising technical effect as the fragments described in the examples. Thus, these fragments would be considered as arbitrarily selected. Therefore, only subject-matter based on SEQ ID NO:1 and 2 and specific fragments thereof could be considered inventive.

4.5 The nucleic acid sequence according to claim 3 comprising a fragment of SEQ ID NO:1 could also be understood as a sequence comprising the promoter sequence but lacking any of the hsp70 encoding sequence. The chimeric sequences would therefore be understood as sequences comprising the promoter and an

(heterologous) antigenic sequence. As it is not apparent what surprising technical effect is achieved by the use of the Arthrobacter hsp70 promoter, it is considered as a mere alternative or a modification of known expression vectors for the recombinant production of antigens would render the subject-matter of claim 4 and 5 obvious. D5 and D6 describes the recombinant production of VP2 of IPNV and of OspA of P.salmonis, respectively (D5: p.206, 2nd paragraph; D7: p.2340, 2. paragraph). Thus, the subject-matter based on the promoter fused to a heterologous antigen is considered obvious over D5 or D7 (see claims 4 to 8, 18, 19, 20, 25 to 27).

4.6 Claim 15 is directed to a fusion protein comprising a fragment or derivative according to claim 11 and an amino acid sequence of a ISAV protein. ISAV proteins are disclosed by D6. Derivatives of hsp70 and fusion proteins thereof were disclosed by D1. Thus, in view of the combination of D1 and D6 the subject-matter of claim 15 is considered an obvious design option.

4.7 Claim 28 refers to an isolated heat shock protein which is defined by the molecular weight its source and an N-terminal amino acid sequence. The only features differentiating it from the prior art, e.g. from other mycobacterial hsp70 proteins (see e.g. D2) appears to be a single amino acid substitution (serine at pos. 2 instead of alanine) and its source. However, it is not apparent how these features can be causative for any relevant technical effect. Thus, it appears that this claim lacks essential technical features such as the full-length amino acid sequence.

4.8 Claim 29 is directed to a DNA expression vector comprising the promoter sequence of SEQ ID NO:1 or a "substantially homologous" sequence, linked to a heterologous gene. It is not apparent which technical problem is solved by this DNA expression vector. A number of DNA expression vectors are known, even comprising a promoter of other heat shock proteins (D8). Thus the vector according to claim 29 could at best be considered as an alternative without any surprising technical effect.

4.9 Thus, the subject-matter of claims 1 to 30 of the present application cannot be considered inventive in the sense of Article 33(3) PCT.